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African-American and caucasian women with newly diagnosed breast cancer were enrolled in the study. Upon enrollment, demographic data, tumor characteristics, and tumor staging data were obtained. Tumor samples were evaluated for estrogen and progesterone receptor levels, DNA ploidy, S-phase fraction, HER-2/*neu* expression, p53 protein accumulation, cathepsin D levels, and glutathione levels. Treatment choices, treatment received, relapse site and date, and date and cause of death were recorded in follow-up. To date, 119 women have been enrolled in the study (61 black and 58 white). While there have been differences between the black and white women noted in some of the above described parameters, none, as yet, reaches statistical significance. Specifically, black women appear to have earlier stage disease at diagnosis, are less likely to have ER/PR (+) tumors, and are more likely to receive appropriate therapy. Despite the relatively favorable findings in black women, their overall survival is significantly worse than that of the white women enrolled in the study.

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Introduction

Breast cancer is the most common invasive malignancy affecting American women, accounting for 28% of all tumors diagnosed in this group.[1] It is also a leading cause of cancer related death in the United States. Although the age-adjusted incidence of breast cancer in black women in the U.S. is less than that seen in white women, the mortality rates observed in blacks and whites are virtually identical.[2] This discrepancy is the result of a significantly lower five year survival rate for black women when compared to white women with breast cancer. The most recent results from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute have documented an 80% five year relative survival for white women diagnosed with breast cancer between 1983 and 1989; the corresponding rate for black women was only 64%.[3] While improvements in the detection and treatment of breast cancer over the last 30 years have led to an improved five year relative survival, there is no evidence that these advances have had an influence on the racial differences in survival.

In order to improve the survival of black women with breast cancer, an understanding of the factors which contribute to their poorer prognosis is necessary. It is known that black women generally have more advanced disease than white women at the time of initial presentation. A tendency toward larger primary tumors as well as a lower incidence of disease confined to the breast and a higher incidence of distant metastases at the time of diagnosis have been documented.[3-13] Environmental, behavioral, and biological factors have also been used to explain the higher incidence of advanced disease in black women with breast cancer. In particular, attention has focused on issues relating to access to medical care and preventive health services. The use of screening mammography has not been shown to be significantly different between healthy black and white women, although the only study of racial differences in breast cancer that has addressed this issue has noted a lower incidence of prior mammography in black women with breast cancer than in their white counterparts.[12,14] Black women with breast cancer have been found to more often rely on hospital-based or public clinics for their health care, and have been noted by some investigators to have a longer interval between symptom recognition and medical consultation.[7,15-17] The difference in median time to medical consultation between black and white women has generally been short, however, and has not adequately explained the significant difference in stage of disease at presentation.

There are also several biological differences in breast cancers of black and white women which may contribute to the differences in disease stage and survival seen in these populations. There is an increased incidence of medullary carcinoma among black women, accounting for 6-9% of all breast cancers, compared to white women, where this tumor histology is seen in 2-3% of women.[2,6,18] Black women have also been noted to have a higher incidence of poorly differentiated tumors of the breast, whether evaluated by architectural grade or nuclear grade, and in one large study higher grade tumors were significantly correlated with disease of more advanced stage.[5,12,19] A majority of studies which have compared hormone receptor levels in black and white women have documented a lower than expected incidence of estrogen receptor positive tumors in black

women with breast cancer.[5,6,12,14,19-23] One group of investigators has examined some of the more recently identified markers of breast tumor biology, including DNA ploidy, S-phase fraction, HER-2/*neu* protein levels and p53 protein accumulation. (52) White women had a significantly lower S-phase fraction than either the black or Hispanic populations.[24] This finding is not unexpected in light of the higher frequency of poorly differentiated tumors in African American women. The Black/White Cancer Survival Study, the most comprehensive study to date of racial survival differences in breast cancer found that tumor biologic characteristics (tumor grade and hormone receptor status) were second only to tumor stage in contributing to the observed survival difference.[25]

There are a limited number of studies which have evaluated the treatment of breast cancer in African American women. The Black/White Cancer Survival Study Group has reported that in women of equivalent stage, black women were just as likely to have surgical therapy as part of their primary treatment plan as white women. (73) They did find that black women were less likely to have breast conserving surgery and more likely to have a modified radical mastectomy.[26] The use of systemic adjuvant therapy, either chemotherapy or endocrine therapy has generally not been found to vary significantly according to race, although the data in this area is quite limited.[24,27-9] Even less information is available regarding the efficacy of systemic therapy in preventing relapse or improving survival in African American women with breast cancer. One study, presented only in abstract form, suggested that black women enrolled on Eastern Cooperative Oncology Group chemotherapy studies for breast cancer had a poorer survival than matched controls, although there is not enough information presented to adequately analyze the reported findings.[30]

Confounding all of this information is the issue of socioeconomic status and its close correlation with race. Observed differences in outcome, particularly if influenced by access to medical care, could certainly be a result of socioeconomics and not race. Attempts to control for socioeconomic factors (performed indirectly using census tract data) have not resulted in uniform agreement. Some studies have demonstrated a disappearance of racial differences in survival while others continue to show a significant impact of race upon survival with breast cancer.[7,11,31-4] Notably, the only prospective study which has collected socioeconomic data from individual patients demonstrated a continued effect of race on stage of disease at presentation.[12] In addition, the noted differences in tumor biology (histology, tumor grade, and hormone receptor status) are less easily explained solely by socioeconomic issues and thus raise the possibility of other factors significantly contributing to the observed survival difference.

We have initiated a prospective study evaluating the clinical, pathologic, and biologic characteristics of newly diagnosed breast cancers in a racially mixed, socioeconomically uniform cohort of patients seen at Truman Medical Center, the public hospital for Kansas City, Missouri. The objectives of the study are: 1) to determine if there are significant differences in breast cancer characteristics at presentation, prognostic factors, or treatment which could explain the survival differences noted between black and white women with the disease and 2) to determine if any documented differences are correlated with the survival of the women in the study.

Methods

Eligibility criteria. The study is being conducted at Truman Medical Center, the public hospital for Kansas City, Missouri. Women who meet the following eligibility requirements are being prospectively enrolled: 1) histologically confirmed invasive adenocarcinoma of the breast, 2) primary surgical therapy for the breast cancer performed at Truman Medical Center, 3) women of African-American or white ethnic background, 4) no prior exposure to radiation therapy or chemotherapy, and 5) written informed consent.

Demographic data. After study enrollment, demographic information is obtained, including age, race, menstrual history, estrogen exposure, family history of cancer, nutritional measurements, and weekly alcohol consumption.

Tumor analysis. Tumor tissue was obtained from either breast biopsy or mastectomy specimens, after gross examination by a pathologist, and tissue was placed in zinc-buffered formalin for routine histology, frozen for routine quantitative estrogen and progesterone receptor analysis, and sent fresh for drug metabolism parameters. Hematoxylin and eosin stained sections will be examined, and the tumors classified according to the criteria of the World Health Organization. Pathologic stages are defined according to the TNM classification.

DNA ploidy, cell cycle analysis, HER-2/*neu* protein content, p53 protein content, and cathepsin D levels were assessed by immunohistochemical analysis of paraffin embedded tissue. This analysis was performed by an outside reference laboratory with extensive experience in the area of cancer immunohistochemistry (Dianon Laboratories, Stratford, CT) using standard techniques.

HER-2/*neu* DNA amplification was determined by Southern blot analysis as described by Herold and Rothberg.[35] The pCER204 probe will be used for this purpose.[36]

Neovascularization in the tumor was evaluated in paraffin-embedded tissue primarily fixed in zinc-buffered formalin. Endothelial cells were stained using antisera against Factor VIII (Dako Polyclonal, Santa Barbara, CA) and the avidin-biotin peroxidase method. Representative areas of the tumor were selected, and microvessel density was assessed using MacMeasure morphometry software (Wayne Rasband, Research Services Branch, NIMH) and a microdigipad (GTCO, Bethesda, MD) with tracings of eighteen x400 photomicrographs of representative areas of each tumor.

Tumor drug metabolism parameters were assessed using fresh tissue. Fresh tumor specimens (at least 500 mg) were minced into small, 2-3 mm pieces and washed twice with cold isotonic saline.Glutathione (GSH) levels were determined in tissue extracts by a specific, and sensitive fluorometric assay using o-phthaladehyde as the fluorescent agent, as described by Hissin and Hilf.[37] GSH concentration will be expressed based on milligram protein and milligram DNA.

Patient follow-up. Breast cancer treatment recommendations and treatment received were recorded for each patient by review of the medical record. Patient outcome data including response to therapy, time to relapse, and survival were also obtained by review of the medical record.

Statistical analysis. Differences between blacks and whites in categorical breast cancer biologic characteristics will be analyzed by a chi-square test for independence. Continuous variables will be evaluated by the Student's t test and/or Mann-Whitney U test for ranked data. Relapse-free survival and overall survival will be estimated using the Kaplan-Meier product limit method, with differences in survival between black and white patients assessed by a log rank test.

Results

As of June 1, 1996, 119 women have been enrolled in the study, 61 black women and 58 white women. The average age of the women enrolled in the study is 55 years. An equal proportion of white and black women were postmenopausal (69%). Tumor stage at the time of diagnosis is outlined in the table below. There were no significant differences in stage at presentation, although black women did appear to have a higher incidence of the smallest (T_1) primary tumors compared to the white women in this study. Lymph nodes were involved in an approximately equal number of women and the median number of positive nodes was 3 for both the black and white women. An equal number of black and white women had distant metastatic disease at the time of diagnosis.

Tumor Stage	**Black (61)**	**White (58)**
T stage	%	%
T_0	1.6	0
T_1	37.7	24.1
T_2	31.1	48.3
T_3	21.3	19.0
T_4	6.6	8.6
T_x	1.6	0
Axillary nodes		
(-)	44.3	39.7
(+)	44.3	51.7
Unknown	11.5	8.6
Metastases		
Yes	9.8	12.1

	Black	White
Overall AJCC Stage		
I	29.5	15.5
IIA	26.2	29.3
IIB	16.4	29.3
IIIA	13.1	8.6
IIIB	4.9	5.2
IV	9.8	12.1

The predominant histologic type in both racial groups was ductal carcinoma, as expected, seen in 79% of black women and 93% of white women.

Tumor biologic characteristics have been analyzed in the 119 women enrolled to date. The table below summarizes these results. None of the differences noted between black and white women reach the level of statistical significance ($p = 0.05$) in univariate analysis at this time.

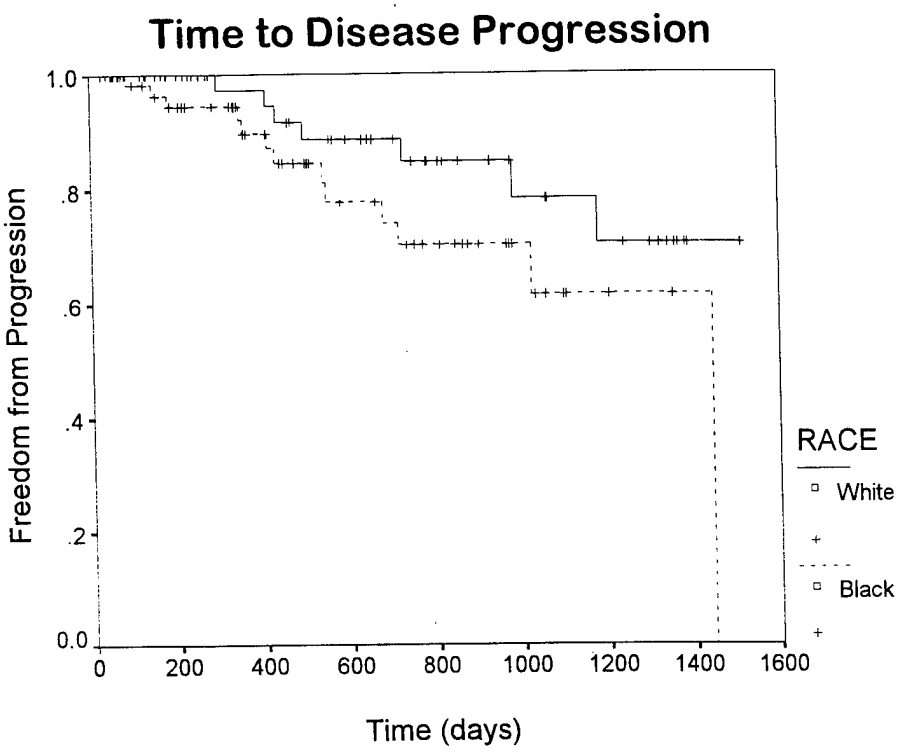
Tumor Characteristic	Black	White
ER (+)	53.7%	66.7%
PR (+)	48.1%	62.7%
DNA index aneuploid	34.4%	37.9%
S-phase fraction	11.2%	11.5%
HER-2/*neu* expression	52.5%	50.0%
p53 expression	47.5%	58.6%
Cathepsin D expression	73.8%	82.8%
Mean microvessel density	11.54	13.35
Glutathione levels (pmol/μprotein)	9.71	11.89

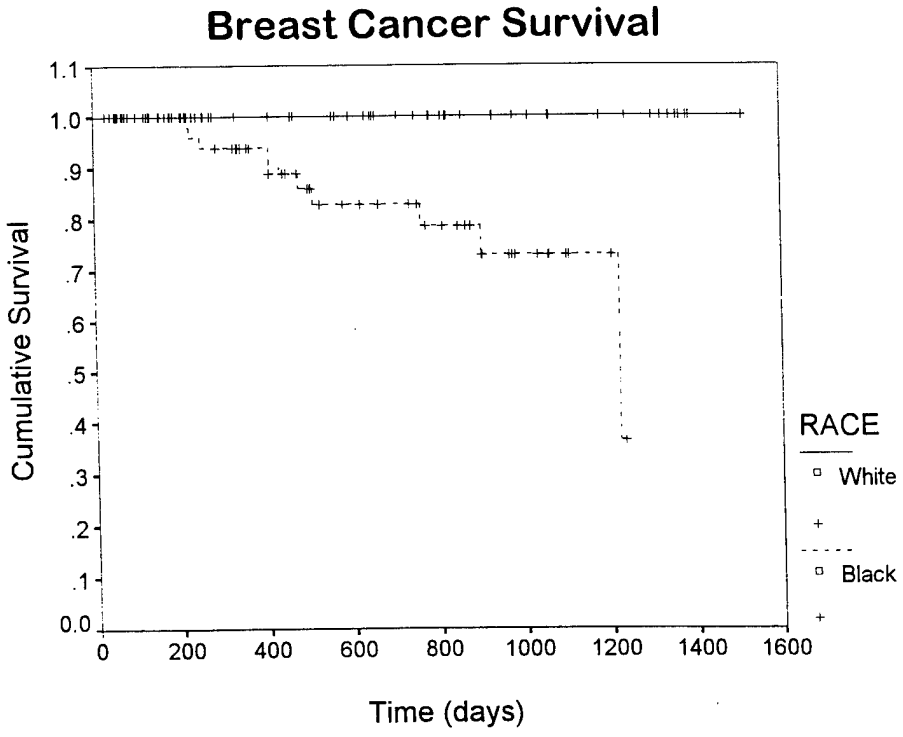
Only preliminary data is currently available regarding treatment choices in the management of breast cancer in our patient population. Eighty-one percent of white women and 69% of black women had a modified radical mastectomy. Breast conserving surgery was performed in 21% of black women and 10% of white women. Thirty-three percent of all women have received breast radiotherapy after the primary surgery with no difference observed in black and white women. Chemotherapy was used in 52% of white women and 41% of black women, and hormonal therapy was used in 50% of white women and 55% of black women. Overall therapy was judged to be adequate for disease stage

in 74% of white women and 84% of black women. It is important to note that this information is incomplete, as many of the enrolled women are still receiving adjuvant therapy.

The estimated three year freedom from progression rate is 73% in black women and 88% in white women (see figure to the right). These time to disease progression curves were not significantly different by log rank comparison ($p = 0.11$).

The estimated three year survival rate is 84% in black women and 100% in white women (see figure in lower right). The survival curves are significantly different by log rank comparison ($p = 0.0006$). Overall, 10 of 61 black women have died and none of the 58 white women have died.





Conclusions

To date, patient accrual and sample processing has gone very smoothly. As a result, there is currently no need to modify the investigational approach. Patient enrollment goals are on schedule, and the planned accrual of 200 patients should be met in 1998. It is clear, however, that data collection will not be complete for approximately

one year after the termination of accrual, as treatment assessment cannot be adequately made until the completion of adjuvant therapy.

The number of patients in the study is too small to make any firm conclusions about differences in breast cancer between black and white women. Several interesting trends can be noted, however. Black women have a higher incidence of T_1 tumors and, as a result, a higher incidence of Stage I cancer. Many of these small tumors were discovered on routine screening mammography and this disparity in the prevalence of the smallest cancers raises the question of a difference in mammographic screening practices between black and white women at our institution. A prospective study evaluating screening practices in the general medicine clinics at Truman Medical Center did not reveal any differences in screening practices between black and white women (unpublished data). While most of the black woman in our study received their primary care in the general medicine clinics at Truman Medical Center or one of several community based clinics in central Kansas City, a significant minority of the white women in our study received their primary care at the public hospital in eastern Jackson County which serves a more rural/suburban indigent population. Screening rates at this institution have not been evaluated yet, but if they are lower than that seen at the primary hospital, this institutional difference in screening practice may explain the apparent racial difference in stage at presentation.

The expected difference in hormone receptor levels is being observed, but is not at a level to reach statistical significance at this time. While there are some racial differences noted in several of the studied prognostic factors, it is too early to tell if these trends will continue.

Treatment appears to be similar for black and white women. The rates of breast conserving surgery in black and white women continue to be low, but have increased since the first interim analysis one year ago. Use of radiation therapy, chemotherapy, and hormonal therapy is similar for black and white women. Black women had a slightly higher rate of receiving overall "adequate" therapy (84% vs. 74%), but these differences are of unclear importance, as many women are still receiving treatment. In addition, a more rigorous assessment of treatment, evaluating dose intensity of chemotherapy delivered, compliance with hormonal therapy, and compliance with radiation therapy is still under study.

Finally, of particular interest, is the initial assessment of freedom from progression and overall survival. In both of these analyses, black women experienced a worse outcome than the white women enrolled in the study. This is despite trends towards earlier stage disease at diagnosis in black women and a higher rate of appropriate breast cancer therapy. The explanation for this difference is not yet clear. Underlying medical conditions have been reported to influence outcome in black women with breast cancer[25], but only one of the eleven black women who have died did not die from recurrent breast cancer. Possibly a more detailed analysis of treatment delivered, including an assessment of response to therapy for recurrent disease will uncover an explanation for the for the survival difference that we are observing. This analysis will be undertaken over the next six months. In addition, it is still early in the study and substantial changes in the survival curves may be observed with further follow-up.

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